REMARKS

Applicant respectfully requests entry of the amendments and the following remarks into the record of the above-identified patent application. Claims 21, 22, 24-29, 31-42 are pending in this application upon entry of the amendments. Claims 1-20 have been withdrawn without prejudice and claims 23, 30, and 43-46 have been canceled without prejudice. Applicant reserves the right to file one or more divisional, continuation, or continuation-in-part applications to any canceled or withdrawn subject matter. Applicant has amended claims 21, 22, 29, 31, 35, 37, 41, and 42 to more clearly recite the claimed invention. Applicant has also amended the specification to correct typographical errors. No new matter has been added by any of the amendments.

I. Information Disclosure Statement

According to page 2 of the office action, the Information Disclosure Statement filed December 5, 2003, excludes pages 347 and 351 of the Yong Sung Choi reference.

Applicant respectfully submits that as disclosed on the List of References Cited By The Applicant, which was submitted with the Information Disclosure Statement, dated December 5, 2003, only page 347 was excluded; page 351 was included with this submission. For the Examiner's convenience, Applicant includes herewith a Supplemental Information Disclosure Statement resubmitting pages 345-346 and 348-351 of the Yong Sung Choi reference.

II. The Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 21-29 and 31-42 are rejected on pages 4-9 of the office action under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant respectfully submits that having amended claims 21, 22, 29, 35, 37-42 the rejections to claims 21-29 and 31-42 have been overcome. Applicant notes that on page 5 of the office action, it was alleged:

> Claim 21 is vague and indefinite in reciting, 'detecting the released antibodies or parts thereof in a sample containing lymphocytes that have been disrupted' because it appears to imply, but fails to clearly define that the antibodies to be detected are limited to those released from disrupted lymphocytes. Perhaps, Applicant intends, 'detecting released antibodies from disrupted lymphocytes contained in a sample.'
> Claim 21 is confusing in reciting, 'lymphocytes which have been disrupted' because it is unclear as to whether disruption of lymphocytes should be part of the method.

Applicant respectfully submits that the rejection to claim 21 appears to be due to the fact that this claim does not explicitly recite the step of disrupting the lymphocytes. This step was deliberately omitted from claim 21 as this claim is intended to encompass the detection step. Claim 22 includes the step of disrupting the lymphocytes. Applicant has amended claim 21 to recite detecting said target antibodies or parts thereof "released from disrupted lymphocytes contained in said sample," thus partially incorporating the Examiner's suggestion. This amendment makes it clear that the antibodies that are detected are from the disrupted lymphocytes.

III. The Rejections Under 35 U.S.C. § 102(b)

Claims 21-23, 26, 33, 35, and 36 are rejected on pages 9-10 under 35 U.S.C. § 102(b) as allegedly being anticipated by Choi (Biosynthesis and Secretion of Immunoglobulins, Immunoglobulins, pages 345, 346, 348-351 (1981)) ("Choi").

Claims 21-23, 25-29, 31, and 33-42 are rejected on pages 10-11 under 35 U.S.C. § 102(b) as allegedly being anticipated by Atkinson et al. (Direct Measurement of Antibody Production in Cell Suspensions using ELISA, Journal of Immunological Methods 76: 365-373 (1985)) ("Atkinson").

Applicant respectfully traverses this rejection for the following reasons.

Anticipation is established when a single prior art reference, published more than one year prior to the earliest applicable priority date of the subject patent, discloses, expressly or under principles of inherency, each and every element of a claimed

invention. *EMI Group N. Am. v. Cypress Semiconductor*, 268 F.3d 1342, 1350 (Fed. Cir. 2001); *Telemac Cellular Corp. v. Topp Telecom Inc.*, 247 F.3d 1316, 1327 (Fed. Cir. 2001); *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). It is settled law that a prior art reference must disclose all of the elements of a claim in order to anticipate the invention recited by that claim. *See Manual of Patent Examining Procedure* § 2131. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

Although Applicant respectfully submits that claim 21 before amendment is novel over each of Choi and Atkinson, Applicant has amended claim 21 to recite that the "body fluid sample is a blood sample or a lymphocyte preparation prepared from said blood sample." Applicant respectfully submits that nowhere does Choi or Atkinson disclose the use of blood. Therefore, because Choi and Atkinson do not disclose each and every element of the claimed invention, Applicant respectfully submits that the rejections under 35 U.S.C. § 102(b) should be withdrawn.

For the above reasons, Applicant respectfully submits that the rejection of claims 21-23, 26, 33, 35, and 36 over Choi and the rejection of claims 21-23, 25-29, 31, and 33-42 over Atkinson have been overcome and should therefore be withdrawn.

IV. The Rejections Under 35 U.S.C. § 103

A. The Rejections

Claim 24 is rejected on pages 11-12 under 35 U.S.C. § 103(a) as allegedly obvious over Choi or Atkinson in view of Cox et al., Kinetics Of Early Immune Response Induced After Parenteral Influenza Vaccination, Options For The Control Of Influenza III, 561-571 (1996)) ("Cox").

Claims 24 and 32 are rejected on pages 13-14 under 35 U.S.C. § 103(a) as allegedly obvious over Choi or Atkinson in view of Cox and in view of Sison A V

(Laboratory Methods for early detection of HIV-type-1 in Newborns and Infants, (Clinical Microbiology Reviews, 5(3): pp. 238-247 (July 1992)) ("Sison").

Applicant respectfully traverses this rejection for the following reasons.

B. The Legal Standards

The Federal Circuit has set forth three basic criteria that must be met to establish a case of *prima facia* obviousness. First, there must have been at the time of the invention a motivation to combine or modify the teachings of the references cited. *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (holding obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination); *see also In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (holding that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art). Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka*, 490 F.2d 488 (CCPA 1974) (holding that to establish *prima facia* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art); *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (holding that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure). Third, there must have been at the time of the invention a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-1208 (Fed. Cir. 1991), *cert. denied* 502 U.S. 856 (1991) (holding that obviousness requires references to show that there was, at the time of the invention, a reasonable expectation of success).

C. The Rejection of Claim 24 Over Choi or Atkinson in view of Cox Should be Withdrawn

The office action alleges that Choi and Atkinson differ from the instant invention in failing to teach detecting newly synthesized antibody in peripheral blood samples. The office action then states that Cox studies kinetics of early immune response induced after immunogen exposure (parenteral influenza vaccination) and use different samples including peripheral blood, serum, and oral fluid. The office action alleges that in the study, *in vitro* cultures of peripheral blood lymphocytes were obtained and tested for antibody response to the immunogen exposure by detecting or determining for the presence of IgG, IgM, and IgA in the sample. According to the office action, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to perform the method as taught by Choi or Atkinson on peripheral blood samples as taught by Cox because Cox provided that lymphocytes used in the method of Choi and Atkinson, can be obtained and cultured from peripheral blood samples for use in testing antibody production in response to parenteral influenza vaccination; hence, peripheral blood appears to constitute an obvious variation of sample routinely used in the art, upon which lymphocytic cells can be obtained for use in antibody production assays.

Applicant respectfully submits that the pending claims encompasses the detection of "newly synthesised antibodies." Prior to this invention being made, it was not disclosed or suggested that such antibodies existed in lymphocytes in any significant amount prior to secretion, nor was it disclosed or suggested that lysis of lymphocytes could yield enough antibody for it to be detected to provide diagnostically useful information. As a consequence, all known assays to detect antibodies were, in general, conducted using long incubation times *in vitro*, where isolated lymphocytes were usually incubated at 37 °C with antigen and the secretion of antibody in response to this antigen, generated during this long, *in vitro* incubation period was detected over time (*see e.g.* Atkinson). The incubation steps are used *in vitro* to allow the accumulation of sufficient antibodies for their detection. One example of such an assay can be found in Atkinson. Atkinson is directed to measurement of *in vitro* secreted antibodies using ELISA. The

disclosure of Atkinson as a whole is directed to the development and validation of a technique for the measurement of antibody that is secreted from cell suspensions during a 6 hour incubation and not to newly synthesized antibody as required by the claims of the present application. This is evident from the paragraph bridging pages 366 and 367, which describes how secreted antibody may be measured in plasma and the paragraph bridging pages 367 and 368 which describes how to modify the ELISA when cell suspensions are used. Furthermore, in the results section it is clear that the assay for in vitro antibody production uses cell suspensions (line 1 of the first paragraph of the Results, Figure 1 and line 1 of the Discussion). At no point do any of the cited documents disclose or suggest that antibodies within the cell comprise a measurable or important population. The invention encompassing detecting "newly synthesized antibodies" derived from disrupted lymphocytes represents a considerable advance in the art and numerous advantages such as those set out on page 4 to page 5, line 16 of the specification enforce this fact.

Applicant respectfully submits that the rejection to claims 24 should be withdrawn.

D. The Rejection of Claims 24 and 32 Over Choi or Atkinson in view of Cox or Sosin Should be Withdrawn

The office action alleges that Sison teaches determining *in vitro* antibody production and using ELISA spot assay to test for immunogenic exposure of infant or neonate to the HIV-1 virus. The office action states that Sison teaches obtaining peripheral blood lymphocytes from infants, isolating and culturing the lymphocytic cells *in vitro,* subjecting the cells to immunogen activation (*i.e.*, pokeweed) and detecting for the production or presence of anti-HIV-1 antibody using HIV-1 antigen coated solid phase (polystyrene wells). The office action then states that Sison uses this test to distinguish between newly synthesized antibodies from the infant and transferred maternal antibodies during pregnancy. According to the office action, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to detect

newly synthesized antibodies using the method taught by Choi or Atkinson on neonatal or infant samples as taught by Sison because Choi and Atkinson specifically taught that their methods specifically detect biosynthesis of antibodies in specific cells such as those that are derived from neonatal cells as in the teaching of Sison, where he specifically emphasized the need to separate and distinguish between neonatal derived antibodies and maternally transferred antibodies. The office action alleges that one of ordinary skill in the art at the time of the instant invention would have been motivated to detect for the presence of newly synthesized antibody using the method of Choi or Atkinson, in samples obtained from infants or neonates as taught by Sison, because Sison specifically taught that antibody production, i.e. of newly synthesized antibodies, in neonatal [lymphocytic] cells provides specific diagnostic information on immunogen exposure and infection for infants.

The Examiner refers to the fact that Atkinson disrupts spleen or lymph node cells to release newly synthesized antibodies. It should however be noted, as mentioned above that the predominant methods used involve no such lysis. Lysis is performed in only a single isolated control experiment to determine if antibody secretion is blocked by puromycin. This control showed that secretion was unaffected. As such this control method is not a method which is taught as being relevant or of interest for further development. The significance of antibodies, which have not been secreted is simply not recognized. As such there would be no motivation to repeat the lysis method or carry it out on any other sample. Thus with regard to the combination of the teaching of Atkinson, the secretion based technique that is the subject of the Atkinson disclosure does not detect newly synthesized antibodies, and as such the combination of Atkinson with Cox does not lead to a method that falls within the scope of the claims of the present application.

With respect to the specific combination of Choi with Cox, even assuming *arguendo* one of ordinary skill in the art had a motivation to combine the teachings of the references, the combination of the teaching of these two references would not lead to a method falling within the scope of the claims since carrying out the method of Choi

irrespective of the sample that is used, does not lead to the detection of newly synthesized antibodies as claimed. Only antibodies that are synthesized *in vitro* are detected using the Choi method. As such, the combination of Choi with Cox cannot does not render claims 24 and 32 obvious.

Moreover, the office action states that Sison teaches obtaining peripheral blood lymphocytes from infants, isolating and culturing the lymphocytic cells *in vitro,* subjecting the cells to immunogen activation (*i.e.*, pokeweed) and detecting for the production or presence of anti-HIV-1 antibody using HIV-1 antigen coated solid phase (polystyrene wells) (emphasis added). The Examiner specifically comments that this document is concerned with the detection of antibody synthesis which occurs *in vitro*, which clearly does not involve newly synthesized antibodies.

Applicant respectfully submits that the rejection to claims 24 and 32 should be withdrawn.

With the exception of extension of time fees, no fee is believed due for this submission. However, except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,

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